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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FRAZIER, BARBARA S	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,759	KIM ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,31 and 32* is/are pending in the application.

4a) Of the above claim(s) *31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27, 31, and 32 are pending in this application.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-20, in the reply filed on 10/22/08 is acknowledged.

3. An examination of prior art has revealed that Groups I and II are obvious variants; accordingly, the examination has been extended to include Group II (claims 21-27).

4. Claims 31 and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/22/08.

5. Claims 1-27 are examined.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh et al (WO 02/16318, cited on Applicant's IDS filed 3/5/07) in view of Loftsson et al (J.Pharm. Sci., 85(10), pp. 1017-1025, 1996, cited in the previous Office action mailed 9/22/08) and Rajewski et al (J. Pharm. Sci., 85(11) pp. 1142-1169, 1996, cited on Applicant's IDS filed 3/5/07).

The claimed invention is drawn to a pharmaceutical composition comprising a thiourea of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt

thereof; and a cyclodextrin or its derivative (see claim 1). The compositions may be in the form of an inclusion complex (e.g., see claim 21).

Suh et al teach thiourea derivatives and pharmaceutical composition containing the same (abstract), including the thiourea derivatives of the claimed invention, such as 1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl) thiourea (for example, see page 238). The composition can contain pharmaceutically acceptable carriers (page 44).

Suh et al do not specifically teach that the carrier is cyclodextrin or its derivative.

Loftsson et al teach that cyclodextrins have been recognized as useful pharmaceutical excipients. Loftsson et al further teach that inclusion complexes formed from a drug and cyclodextrin offer a variety of physiochemical advantages over the unmanipulated drugs including increased water solubility and solution stability (abstract).

Additionally or alternatively, Rajewski et al teach that inclusions complexes formed by a cyclodextrin and a drug can be used to increase solubility and dissolution rate, decrease volatility, alter release rates, modify local irritation, and increase the stability of drugs (page 1142). Loftsson et al further teach that drugs with lower aqueous solubility have a greater relative solubility enhancement obtained through cyclodextrin complexation (page 1020, 2nd column).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select a cyclodextrin as the carrier in the compositions of Suh et al; thus arriving at the claimed invention. One skilled in the art would be

motivated to do so because the use of a cyclodextrin as the carriers provides the advantages of increased solubility and dissolution rate, decreased volatility, altered release rates, decrease in local irritation, and increased stability of drugs, as taught by Loftsson et al and Rajewski et al. One would reasonably expect success from the use of a cyclodextrin as a carrier in the composition of Suh et al because cyclodextrins are known to work well with compounds which are hardly water-soluble, as taught by Loftsson et al.

Regarding claims 2, 3, 22, and 23, Suh et al specifically teach the compounds of the claimed invention (see page 238).

Regarding claims 4 and 24, Rajewski et al teach that most pharmaceutical agent form 1:1 complexes with cyclodextrin, while higher order complexes are also possible (page 1143).

Regarding claims 5-7 and 25-27, Loftsson et al teach that most cyclodextrins are alpha-, beta-, and gamma-cyclodextrin (page 1017), and Rajewski et al teach the use of various beta-cyclodextrins, including 2-hydroxypropyl-beta-cyclodextrin (see Table 1 and page 1145).

Regarding claims 8 and 9, Suh et al teach that the compositions may contain pharmaceutically acceptable diluents (page 44).

Regarding claim 10, Loftsson et al teach the formation of an inclusion complex by the addition of the drug to an aqueous cyclodextrin solution to form a drug-cyclodextrin complex solution (abstract and page 1020).

Regarding claims 11-13, Loftsson et al teach that the solid formulations of the drug-cyclodextrin complex by removal of the water from the aqueous drug-cyclodextrin complex solution (page 1020). It is noted that claim 11 appears to be a product-by-process. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113. Since the limitations of claims 11-13 directed to the particular steps of solvent choice and drying step to remove the solvent do not impart a structural limitation to the compositions of said claims, they are not given patentable weight.

Regarding claim 14, Suh et al teach that the compositions are useful for treating disorders identical to those recited in claim 14 (see abstract).

Regarding the type of formulation (claims 15-20), Rajewski et al teach that drug-cyclodextrin complexes may be in formulations for oral (pages 1150-1155), parenteral, (including intravenous and intramuscular dosing) (pages 1145-1150), transdermal (pages 1162-1164), transocular (pages 1155-1159), transnasal (pages 1159-1162), and intrarectal use (pages 1164-1165).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-22 of copending Application No. 11/727,413 in view of Loftsson et al (J.Pharm. Sci., 85(10), pp. 1017-1025, 1996, cited in the previous Office action mailed 9/22/08) or alternatively over Rajewski et al (J. Pharm. Sci., 85(11) pp. 1142-1169, 1996, cited on Applicant's IDS filed 3/5/07).

The claimed invention is delineated above (see paragraph 11).

Copending application '413 claims a pharmaceutical composition comprising a compound which is identical to those of the claimed invention, including 1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl) thiourea (see claim 19), and a pharmaceutically acceptable carrier.

Copending application '413 does not specifically teach that the carrier is a cyclodextrin or its derivative.

Loftsson et al teach that cyclodextrins have been recognized as useful pharmaceutical excipients. Loftsson et al further teach that inclusion complexes formed from a drug and cyclodextrin offer a variety of physiochemical advantages over the unmanipulated drugs including increased water solubility and solution stability

(abstract). Additionally or alternatively, Rajewski et al teach that inclusions complexes formed by a cyclodextrin and a drug can be used to increase solubility and dissolution rate, decrease volatility, alter release rates, modify local irritation, and increase the stability of drugs (page 1142). Loftsson et al further teach that drugs with lower aqueous solubility have a greater relative solubility enhancement obtained through cyclodextrin complexation (page 1020, 2nd column).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select a cyclodextrin as the carrier in the compositions of copending application '413; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because the use of a cyclodextrin as the carriers provides the advantages of increased solubility and dissolution rate, decreased volatility, altered release rates, decrease in local irritation, and increased stability of drugs, as taught by Loftsson et al and Rajewski et al. One would reasonably expect success from the use of a cyclodextrin as a carrier in the composition of copending application '413 because cyclodextrins are known to work well with compounds which are hardly water-soluble, as taught by Loftsson et al.

Regarding the limitations in dependent claims 2-19 and 21-27, said limitations are claimed in claims 19-22 of copending application '413 and in the teachings of Loftsson et al and Rajewski et al as recited above (see paragraph 11).

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611